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Comparison of Estrogen Receptor Assay Results from Pathology Reports with Results from Central Laboratory Testing: Implications for Population-Based Studies of Breast Cancer

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Abstract

Population-based studies of women with breast cancer commonly utilize information culled from pathology reports rather than central pathology review. The reliability of this information, particularly with regard to tumor biomarker results, is of concern. To address this, we evaluated the concordance between estrogen receptor (ER) results as determined from the original pathology reports and ER results obtained on the same specimens following testing in a single laboratory. Tissue microarrays (TMAs) were constructed from paraffin blocks of 3,167 breast cancers that developed in women enrolled in the Nurses' Health Study. ER immunostains were performed on all TMA sections in single run. Results of ER immunostains performed on the TMA sections were compared with ER assay results abstracted from pathology reports. Among 1,851 cases of invasive breast cancer in which both ER results from pathology reports and central ER test results were available, the reported ER status and the ER status as determined from immunostains on TMAs were in agreement in 1,651 cases (87.3 %; kappa value 0.64, $p<0.0001$). When the comparison was restricted to ER assays originally performed by immunohistochemistry, the agreement rate increased to 92.3% (kappa value 0.78, $p<0.0001$). These results provide a framework for the accuracy of ER results abstracted from clinical records. Further, they suggest that utilizing ER assay results from pathology reports is a reasonable, albeit imperfect, alternative to central laboratory ER testing for large, population-based studies of patients with breast cancer.

Large population-based, epidemiologic studies of women with breast cancer commonly utilize information abstracted from pathology reports in lieu of central pathology review. This is due to the practical limitations of performing central pathology review on hundreds to thousands of cases, and to the economic and logistical constraints inherent in obtaining

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breast cancer slides and paraffin blocks from decades past. The reliability of the information contained in breast cancer pathology reports used for this purpose is of concern, since the original misclassification of pathologic features could have a substantial impact on study results. In particular, the impact on epidemiologic studies of using unverified results for estrogen receptor (ER) assays performed at many different institutions with a variety of methods over a long period of time has not been previously evaluated. To address this issue, we compared the results of ER immunostains performed in a central laboratory on sections with results of ER assays abstracted from the corresponding pathology reports of breast cancers from women enrolled in the Nurses' Health Study.

The Nurses' Health Study is an ongoing, prospective cohort study that began in 1976, when 121,700 women who were registered nurses between ages 30 years and 55 years completed a mailed, self-administered questionnaire about their health behaviors, lifestyle factors, and medical histories. Follow-up questionnaires have since been sent to the participants every 2 years to obtain updated information. Tissue microarrays were constructed from paraffin blocks of 3,167 breast cancers that developed between 1976 and 1996 among women enrolled in this study. Three 0.6 mm diameter cores were punched from a representative paraffin block from each case and embedded in recipient paraffin blocks. This resulted in the construction of 24 tissue microarray blocks, each containing 120–160 cases arrayed in triplicate. Immunostaining for ER was performed on 5 μm sections cut from the tissue microarray blocks in a single staining run following heat-induced epitope retrieval. The primary antibody used was a rabbit monoclonal antiobody to ER (clone SP1, Dako, Carpinteria, CA, dilution 1:400). Appropriate positive and negative controls were included in the staining run.

Two of the study pathologists (JM and LC) visually estimated the percentage of tumor cells showing nuclear immunoreactivity for ER in every tissue microarray core. A case was scored as ER-positive when there was staining in more than 10% of the tumor cell nuclei in any of the three cores from that case, low positive when staining was seen in 1 to 10% of nuclei in any of the three cores, and negative when no nuclear staining for ER was seen in any of the three cores. Given that several consensus statements have recommended that any ER staining in a breast cancer is sufficient to categorize tumor as ER-positive (refs), for the purposes of this analysis, positive and low-positive cases were combined into a single "ER-positive" group. Results of the original ER assays were abstracted from pathology reports for each case. Raw concordance data and kappa statistics were used to assess the level of agreement between the ER assay results as determined from the tissue micrrorray sections and the ER status provided in the pathology reports.

Of the 3,167 cases, ER results from the pathology reports and from the tissue microarrays were both available in 1,851 cases; these samples comprise the population for this analysis. The original ER assays had been performed over a 20 year period in laboratories from 34 states in the United States, and in various laboratories in Canada and Saudi Arabia. By report, the ER status was originally assessed using a biochemical assay in …%, an immunohistochemical assay in ..% and an immunoflourescent assay in …..%.

The ER status as abstracted from the pathology reports and the ER status as determined on the tissue microarrays were in agreement in 1,615 of the 1,851 cases (87.3%; kappa value 0.64, $p<0.0001$, Table 1). There were 99 cases (5.3%) in which the reported ER was positive but the tissue microarray ER was negative, and 137 cases (7.4%) in which the reported ER was negative and the tissue microarray ER positive. When the analysis was restricted to the 336 cases in which the original ER status was determined by an immunohistochemical assay, the results of the original ER assay were in agreement with those obtained on the tissue microarrays in 310 cases (92.3 %; kappa value 0.78, $p<0.0001$, Table 2). In this subset, there were 9 cases (2.7%) in which the reported ER was positive but the tissue microarray ER was negative, and 17 cases (5.1%) in which the reported ER was negative and the tissue microarray ER positive.

The practice of using information abstracted from pathology reports for large population-based studies has many logistical and economic advantages over central pathology review. However, these advantages need to be balanced against the potential for misclassification of diagnoses and pathology details when using information abstracted from pathology reports, particularly when they have been collected from many institutions over a long period of time, during which diagnostic criteria, reporting practices and test methodologies have evolved. In fact, prior studies have indicated that there is considerable variation in the content and the quality of the information available in breast cancer pathology reports [8, 9]. Such clinically important elements as margin status, lymphovascular space invasion, and the presence or absence of ductal carcinoma in situ, have not always been well documented. Furthermore, interlaboratory and intralaboratory variation in ER assay methodology and reporting of results has varied considerably since this test was first introduced into clinical practice in the 1970s, raising concerns about the validity of using reported ER results in epidemiologic studies of patients with breast cancer.

In our study, the original ER assays had been performed in numerous laboratories across the U.S., Canada and Saudia Arabia using a wide range of assays over a 20 year period of time. Nonetheless, we found a high level of concordance between ER results abstracted from pathology reports and the results obtained by repeating the ER analysis in a central laboratory at one point in time using immunostains of tissue microarray sections. The results of this study for the first time provide point of reference for the accuracy of ER results abstracted from clinical records. Further, they suggest that utilizing ER assay results from pathology reports is a reasonable, albeit imperfect, alternative to central laboratory ER testing for large, population-based studies of patients with breast cancer.

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Table 1

Comparison of estrogen receptor results using an immunohistochemical assay on tissue microarray sections with results abstracted from pathology reports in 1851 invasive breast cancers.

		TMA Results		
		ER+	**ER−**	**Missing**
Pathology Report	ER+	1310	99	87
	ER−	137	305	35
	Missing	322	137	29

Table 2

Comparison of estrogen receptor results using an immunohistochemical assay on tissue microarray sections with results of immunohistochemical estrogen receptor assays abstracted from pathology reports in 310 invasive breast cancers.

		TMA Results		
		ER+	**ER−**	**Missing**
Pathology Report	ER+	247	9	41
	ER−	17	63	10
	Missing	1505	469	100